REMARKS

Reconsideration and allowance are respectfully requested.

Remarks Regarding Claim Amendments:

The amendments to the claims are fully supported by the Application as originally filed and thus, no new matter is added by their entry. For example, the recitations of claim 14 and 16 are incorporated into amended claim 1. The recitations of claims 8, 9, 14 and 16 are incorporated into claim 4. Claims 2-5, 20, 22, 23 and 28 are amended to remove the word "preferably." Claims 6-7, 11, 18-21, 23-26 and 29-30 are amended to conform to U.S. spelling. Claims 15, 17 and 18 are amended so that they no longer depend on canceled claims. The basis for the amendment to claim 18 may be found in the specification on page 6, lines 11-14. The basis for the amendment to claim 19 may be found on page 8 line 5. No new matter is added by the claim amendments and the entry of the claim amendments is requested.

The issues raised in the instant Office Action are addressed in the order that they appear in the Office Action.

Remarks Regarding Section 102:

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-13, 16-18, 27-29 stand rejected under 35 U.S.C. § 102 as allegedly anticipate by WO 97/04086. Applicants traverse.

Solely in an effort to expedite prosecution, and without addressing the merits of the Examiner's rejection, Applicants amended claim 1 to incorporate the recitations of a claim (claim 14) that has not been rejected as anticipated by WO 97/04086. Since claim 14 is novel over WO 97/04086, amended claim 1 and claims dependent thereon

which incorporated the recitations of claim 14 are also novel over WO 97/04086. Claims 2-13, 16-18 and 27-29 are each either dependent on claim 1 or is canceled.

Thus, for the reasons stated above, claims 1-13, 16-18, 27-29 is not anticipated by WO 97/04086 and the withdrawal of this rejection is requested.

Claims 1-10, 12-13, 16-22 and 27-29 stand rejected under 35 U.S.C. § 102 as allegedly anticipate by U.S. Patent 4,073,687. Applicants traverse.

The claimed invention is not anticipated because U.S. Patent 4,073,687 does not disclose the limitations of the claims. The claimed invention, as amended, is directed to, inter alia, a process performed at a temperature of below 15°C when a wild type acylase is used – see, instant claim 1. In this rejection, the Office Action alleged that Example 7 of U.S. Patent 4,073,687 teaches the claimed process. However, Applicants note that Example 7 of U.S. Patent 4,073,687 uses wild type acylase and a temperature of 30°C. Since U.S. Patent 4,073,687 does not teach a claim limitation of claims 1-10, 12-13, 16-22 and 27-29 (a reaction temperature of below 15°C if wild type acylase is used) there can be no anticipation.

Applicants submit that this feature of their claimed invention is sufficient to distinguish over the cited document so any other incorrect allegations about its disclosure are not disputed here, but the opportunity to dispute them in the future is reserved. Withdrawal of this rejection is requested.

Claims 31-32 stand rejected under 35 U.S.C. § 102 as allegedly anticipate by U.S. Patents 5,034,522, 3,819,620, 5,278,157 or 4,139,702. Applicants traverse.

Solely in an effort to expedite prosecution, Applicants canceled claims 31 and 32. This rejection is moot in view of the claim cancellation and its withdrawal is requested.

Remarks Regarding Section 103:

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396

(2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396.

Claims 19-21 and 23 stand rejected under 35 U.S.C. § 103 as allegedly obvious in view of WO 97/04086 or U.S. Patent 4,073,687.

The claimed invention, as recited in amended claim 1, is directed to a process of producing cephradine under specific conditions. Among other reaction conditions there is a requirement that (a) if a wild tyhpe penicillin acylase is used, the temperature of the reaction should be below 15° C or (b) if an acylase having a higher S/H ratio than wild type acylase is used, the temperature of the reaction should be above 15° C. Applicants want to explain the non-obviousness of the claimed invention by discussion the features (a) and (b), as explained above separately. The basis of non-obviousness may be found in Table 1 (page 15) of the specification.

(a) when the acylase is wild type, the reaction temperature is below 15° C: As shown in the middle column of Table 1, for the wild type acylase, a temperature of 20° C results in a conversion of 68% and a [DH] of 2.97%, whereas at 10/7° C the conversion is 74% and the [DH] is only 0.84%.

(b) when the acylase has a higher S/H ratio than wild type acylase of E. coli and the temperature is at least 15° C: As shown in the bottom row of Table 1, for the wild type E. coli enzyme at 20° C the conversion is 68% and the [DH] is 2.97%. However, for the enzyme with a higher S/H (13.8 vs. 1.8) the conversion is 99.4% and the [DH] is only 0.56%.

Neither WO 97/04086 nor U.S. Patent 4,073,687 teaches or render obvious the claimed invention. That is, neither reference teaches the use of wild type enzyme at a temperature less than 15° C or the use of enzyme with S/H > wild type at a temperature at least 15° C, would result in the formation of cephradine with a [DH] below 2% and a conversion of at least 70%. Thus, for at least this reason, the claimed invention is not rendered obvious in view of WO 97/04086 or U.S. Patent 4,073,687.

Claim 30 stands rejected under 35 U.S.C. § 103 as allegedly obvious in view of

(1) a combination of WO 97/04086 and WO 98/56944 or

(2) a combination of U.S. Patent 4,073,687 and WO 98/56944.

Applicants traverse.

As discussed above, the claimed invention is not obvious in view of WO 97/04086 or U.S. Patent 4,073,687 because neither reference teaches the use of wild type enzyme at a temperature less than 15° C or the use of enzyme with S/H > wild type at a temperature at least 15° C. The addition of WO 98/56944 does not cure this defect. WO 98/56944 is used by the Office Action to show the special feature of using sodium bisulfite. Without addressing the merit of the Office Action's position, Applicants note that like WO 97/04086 or U.S. Patent 4,073,687, WO 98/56944 also do not teach the claimed limitation (the use of wild type enzyme at a temperature less than 15° C or the use of enzyme with S/H > wild type at a temperature at least 15° C). Since a claim recitation is not taught or rendered obvious by any combination of the cited references, the claimed invention is not obvious in view any combination of the cited references.

Claims 1-17, 19-21 and 29 stand rejected under 35 U.S.C. § 103 as allegedly obvious in view of WO 96/02663. Applicants traverse.

WO 96/02663 refers to the synthesis of β-lactams at a constantly high concentration of the parent β-lactam and acylating agent. WO 96/02663 does not mention anywhere in its disclosure, the conversion value or DH value in relation to cephradine synthesis. In particular, WO 96/02663 does not mention that a [DH] value of less than 2% or a conversion of at least 70% can be obtained in any process. In fact, WO 96/02663 teaches away from the claimed invention since, as the Examiner acknowledges, it gives a preferred temperature range of 20-30° C for the wild type E.

coli acylase. In contrast, Applicants' claim 1 recites that when a wild type penicillin acylase is used that the reaction should be carried out at a temperature below 15° C. The skilled person would therefore be dissuaded to try to carry out the reaction with a wild type acylase below 15° C. Thus, WO 96/02663 teaches against claim 1, and claims dependent thereon, because WO 96/02663 teaches the use of a temperature of 20-30° C for the wild type E. coli acylase.

For the reasons stated above, claims 1-17, 19-21 and 29 are not obvious in view of WO 96/02663.

Claims 1-17, 19-21 and 29 stand rejected under 35 U.S.C. § 103 as allegedly obvious in view of WO 99/31109. Applicants traverse.

WO99/31109 refers to complexes of cephradine and cefaclor with 1-naphthol and to the process of making such a complex. In contrast, Applicants' claimed invention is directed to the process for preparing cephradine using a process comprising reacting 7-aminodesacetoxy cephalosporanic acid (7-ADCA) with D-dihydrophenylglycine in activated form (DHa) in the presence of an enzyme in a reaction mixture to form cephradine. See, e.g., instant claim 1. In contrast, Example IV of WO99/31109 cited by the Examiner, the enzymatic synthesis of cefaclor-naphthol complexes is disclosed, not of cefaclor itself, let alone cephradine, the subject of the present invention. In addition, on page 5 of WO99/31109 is stated that the temperature at which the enzymatic reaction is carried out is not particularly critical and is usually lower than 40°C, preferably between -5 and 35°C.

The claimed invention discloses the fact that it is necessary to carefully select the temperature of the synthesis reaction depending on the type of enzyme used therein. This aspect is not disclosed or render obvious by WO99/31109. On the contrary, as summarized above, WO99/31109 states that the temperature is not critical.

For the reasons stated above, Applicants submit that the claimed invention is not obvious in view of WO99/31109.

Withdrawal of all of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Remarks Regarding Section 112:

Claims 1-31 stand rejected under 35 U.S.C. § 112 as allegedly indefinite for 10 reasons listed below. Applicants traverse each of the grounds of rejection. The Examiner's specific rejections and Applicants response are listed below:

1. Claim 4 is allegedly indefinite because the range of parameters being controlled was not specified. This claim has been amended to specifically recite pH and temperature ranges. Thus, this basis for rejection is moot.

2. Claim 29 is allegedly unduly functional and does not recite a temperature range or pH. Claim 29 depends on claim 1 and incorporates the recitations of claim 1 by nature of its dependency. Applicants amended claim 1 to recite a temperature range. Thus, this basis of rejection is moot.

3. Claim 27 is allegedly indefinite because of the term "dissolving" because it is unclear what it is being dissolved into. The claim has been amended to state that dissolving is into the reaction mixture.

4. Claim 27 is allegedly indefinite because of the term "hydrate" In the reaction mixture is unclear because hydrate does not exist until the crystallization process. Claim 27 has been amended to recite that crystallization is performed in the reaction mixture.

5. Claim 1 and 4 are allegedly indefinite because it is unclear because of the phrase "concentration . . . in the reaction mixture is below 2%" does not make it clear whether the concentration is below 2% all of the time. The claims have been amended to state that the concentration is below 2% throughout the reaction.

6. Claim 27 is allegedly indefinite because it is unclear because of the recitation "S/H ratio." Claim 1 is amended to state that the enzyme S/H ratio should be higher than E. coli S/H ratio throughout the reacting step.

7. The claims are allegedly indefinite because it is unclear because of the recitation "preferably." This term has been removed from all the pending claims by amendment and this basis of rejection is moot.

8. Claim 13 is allegedly indefinite because it is unclear because of the recitation "S/H ratio." Since claim 13 is canceled, this basis of rejection is moot.

9. Claim 18 is allegedly indefinite because it is unclear because of the recitation "mutant." Claim 18 is amended to recite that mutant penicillin acylase is derived from a wild type acylase via recombinant DNA methodology by substituting one amino acid residue for a new residue. Since "mutant" is defined in amended claim 18, this basis of rejection is moot.

10. Claim 22 is allegedly indefinite because it is unclear because of the recitation "0%." The Office Action states that if there is no 7-ADCA present, the reaction cannot take place. Applicants note that claim 22 recites that 7-ADCA is between 0% and 5 wt. %. 0% is not claimed since 0% is not between 0% and 5 wt. %. Applicants request that this rejection be withdrawn.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite in view of the claim amendments and arguments above.

Claims 19-21, 23 and 29 stand rejected under 35 U.S.C. § 112 first paragraph as alleged not enabled because the process is for crystallizing cephradine but it is the monohydrate that is actually crystallized. Further, claims 24-26 stand rejected under 35 U.S.C. § 112 first paragraph as alleged not enabled because the claim cites hydrate but example 3 only produce monohydrate. Applicants traverse. Methods for converting the hydration states of chemicals are known and once one hydration state of a chemical is produced, the other hydration states can be made.

Claims 1-30 stand rejected under 35 U.S.C. § 112 first paragraph as alleged not complying with the written description requirement. The Office Action stated that in the

event that Applicants argue that the conversion and concentration of the DH language is a claim limitation, then the claims do not meet the written description requirement because the claims cover all methods of producing the results whereas the claim only recite one method of producing the results – naming by controlling pH and/or the temperature. Applicants traverse.

The claims, as amended, are directed to one method of producing cephradine by adjusting temperature and the acylase used. This method is part of each independent pending claim. Since this method is fully supported by the specification, Applicants submit that the current pending claims, as amended, are fully supported by the specification.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date. Their disclosure would also teach a skilled person, who possesses general knowledge available in the art, how to make and use the claimed invention.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: Eric Sinn

Eric Sinn
Reg. No. 40,177

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100